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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/854,825	05/12/97	CHISARI	F 329368-101CO

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EXAMINER	
PARKIN, J	
ART UNIT	**PAPER NUMBER**
1648	20

DATE MAILED: 04/02/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary	Application No. 08/854,825	Applicant(s) Chisari et al.
	Examiner Jeffrey S. Parkin, Ph.D.	Group Art Unit 1648

X Responsive to communication(s) filed on *30 Aug 2000*

X This action is **FINAL**.

Since this application is in condition for allowance except for formal matters, **prosecution as to the merits** is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

X Claim(s) *22-25, 30, 32, 36, 40, and 44-66* is/are pending in the application

Of the above, claim(s) _____ is/are withdrawn from consideration.

Claim(s) _____ is/are allowed.

X Claim(s) *22-25, 30, 32, 36, 40, and 44-66* is/are rejected.

Claim(s) _____ is/are objected to.

Claims _____ are subject to restriction or election requirement.

Application Papers

See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

The specification is objected to by the Examiner.

The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

All ☐Some* ☐None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

Notice of References Cited, PTO-892

Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

Interview Summary, PTO-413

Notice of Draftsperson's Patent Drawing Review, PTO-948

Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Response to Amendment

Status of the Claims

1. Acknowledgement is hereby made of receipt and entry of the Amendment filed 03 August, 2000, wherein claims 22, 60, and 62 were amended. Claims 22-25, 30, 32, 36, 40, and 44-66 are pending in the instant application.

35 U.S.C. § 112, First Paragraph

2. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 22-25, 30, 32, 36, 40, and 44-66 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *In re Rasmussen*, 650 F.2d 1212, 211 U.S.P.Q. 323 (C.C.P.A. 1981). *In re Wertheim*, 541 F.2d 257, 191 U.S.P.Q. 90 (C.C.P.A. 1976). Applicants traverse and submit that the inventive concept is clearly described in the specification. It was argued that pages 8, 13, and 14 provide support for the claimed invention. Case law was also cited in support of their position. Applicants' arguments have been carefully considered but are not deemed to be persuasive.

Contrary to applicants' assertion, the pages of the specification relied upon fail to provide sufficient support for

the claimed invention. The passages relied upon provide a broad and non-specific disclosure. Nothing contained in these sections would lead the skilled artisan to conclude that applicants were in possession of the claimed invention at the time of filing. Applicants are reminded that the claims are directed toward polypeptides having "**no more than a total of two single amino acid substitutions, deletions, or insertions**". Support for this limitation does not exist. Applicants are invited to identify those portions of the specification that provide direct support for this claim limitation. As previously noted, the disclosure does reference (see p. 14, lines 14-25) functionally equivalent peptides that can be identified through "**suitable single amino acid substitutions, deletions, or insertions**". The disclosure also provides a listing of HCV peptides that may contain CTL epitopes (see p. 44-46), as well as, their further characterization to actually confirm the presence of such epitopes. However, **the disclosure does not describe the preparation of HCV peptidic variants containing no more than a total of two single amino acid substitutions, deletions, or insertions.** Moreover, the courts have repeatedly concluded that a generic or nondescript reference in the specification is insufficient to support a specific species or subspecies. *In re Smith*, 458 F.2d 1389, 1393-94, 173 U.S.P.Q. 679, 684 (C.C.P.A. 1972). *In re Welstead*, 463 F.2d 1110, 1114, 174 U.S.P.Q. 449, 451 (C.C.P.A. 1972). *In re Ruschig*, 379 F.2d 990, 995-96, 154 U.S.P.Q. 118, 123, (C.C.P.A. 1967). Accordingly, the skilled artisan would conclude that applicants were not in possession of the claimed peptidic variants at the time of filing.

4. The previous rejection of claims 22-25, 30, 32, 36, 40, 44-57, and 60-66 under 35 U.S.C. § 112, first paragraph, because the specification does not reasonably enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims, is hereby withdrawn in response to applicants' arguments. Specifically, Reece *et al.* (1993) was cited to illustrate that multipin synthethic peptide screening methods were available at the time of filing to identify and characterize T-cell epitopes.

5. Claims 58 and 59 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants traverse and referencing the "Utility Guidelines" suggest that all that is needed to establish a credible utility is data obtained from an in vitro assay, assuming said assay is reasonably predictive of in vivo activity. Applicants appear to be arguing that an unreasonable burden has been placed upon them to demonstrate that the claimed invention functions as a pharmaceutical. Applicants' arguments have been thoroughly considered but are not deemed to be persuasive.

Applicants are reminded that claims 58 and 59 are drawn toward pharmaceutical compositions **comprising** HCV-specific CTL epitopes. The broadest claim does not place any size constraints on the peptide length. Applicants are advised that the rejection of the claims was clearly set forth under 35 U.S.C. § 112, first paragraph, not 35 U.S.C. § 101. It appears that applicants have erroneously assumed that this is a utility rejection. Applicants are reminded that rejections made under 35 U.S.C. § 112, first paragraph, address different issues from those examined under the utility guidelines. These issues include whether the claims are fully supported by the disclosure (*In re Vaeck*, 947 F.2d 488, 495,

20 U.S.P.Q.2d 1438, 1444 (Fed. Cir. 1991)), whether the applicant has provided an enabling disclosure of the claimed subject matter (*In re Wright*, 999 F.2d 1557, 1561-1562, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993)), and whether the applicant has provided an adequate written description of the invention (*Chemcast Corp. v. Arco Industries Corp.*, 913 F.2d 923, 927-928, 16 U.S.P.Q.2d 1033, 1036-1037 (Fed. Cir. 1990)). Thus, the rejection was properly framed under this statute.

As previously set forth, the claims are directed toward pharmaceutical compositions comprising the claimed HCV CTL epitopes. The term pharmaceutical has an art-recognized definition and pertains to **the use of medicinal drugs to treat disease** (refer to Dorland's medical dictionary, 1988, pp. 1271-1272; *In re Gardner*, 166 U.S.P.Q. 138-142 (1970 C.C.P.A.); *Ex parte Skuballa*, 12 U.S.P.Q.2d 1570 (1989 Bd. Pat. App. Int.)). The specification states (see p. 27, second paragraph) that "the peptides of the present invention as described above will be administered in a pharmaceutical composition to an individual already infected with HCV." The same paragraph further states that "In therapeutic applications, compositions are administered to a patient in an amount sufficient to elicit an effective cytotoxic T lymphocyte response to HCV and to cure or at least partially arrest its symptoms and/or complications." Therefore, it would be reasonable for the skilled artisan to assume that said peptides will be used in the prevention or treatment of HCV infection in humans, which are the natural host of the virus.

The disclosure contains a number of deficiencies that render the claims nonenabled. These were clearly set forth in the last Office action and are again addressed as follows:

1) The disclosure fails to provide any guidance pertaining to the effects of amino acid substitutions, deletions, or insertions on MHC Class I binding activities of the claimed HCV CTL epitopes.

5) The art teaches that virally infected patients contain CTL epitopic variants with reduced HLA and T cell receptor binding capacities. The importance of this statement is that it emphasizes, once again, that minor perturbations in the amino acid sequence can have profound effects on the peptide activity. Applicants have not provided any evidence addressing this concern. Which amino acid substitutions, additions, or deletions can be performed that will result in the retention of the desired immunological properties? The disclosure is silent concerning this topic.

6) The art teaches that natural sequence variation in viruses, particularly in CTL epitopes, results in the generation of immune resistant viruses. Once again, applicants fail to provide any objective scientific evidence that addresses this concern. The skilled artisan requires a knowledge of the molecular determinants modulating the immunogenic and protective or therapeutic properties of any given peptide before a rational sequence can be selected for inclusion in the claimed pharmaceutical composition. Apparently the applicants believe it would be routine experimentation to take the large genus of peptides encompassed by the claim language and blindly administer them to patients in need of such therapies. This approach is simply unreasonably and illogical.

7) The art teaches that HCV-specific CTL may actually contribute to liver disease pathogenesis in chronically infected patients. Applicants again fail to provide any objective scientific evidence or publications that address this concern.

8) The disclosure fails to provide sufficient guidance demonstrating that a vigorous HCV-specific CTL response can be generated in humans, or other mammals, that will result in amelioration of the clinical sequelae associated with HCV infection. Applicants dismiss this concern and state that a therapeutic effect need not be achieved in every patient. This

The prior art clearly illustrates that single amino acid changes can abrogate the binding activities of any given peptide. Applicants have failed to provide any credible scientific evidence addressing this deficiency.

2) The disclosure fails to provide sufficient guidance pertaining to the effects of flanking amino acid residues the immunogenic properties of any given peptide. As previously noted, flanking amino acid sequences can influence the immunologic properties of any given peptide in an unpredictable manner. Epitopes can be destroyed or neoepitopes created. However, applicants have failed to provide any credible scientific evidence addressing this deficiency.

3) The art teaches that the presence of an MHC class I binding motif in a peptide is not sufficient to confer binding to the appropriate class I molecule. Contrary to applicants' assertions, the activities of peptides having two amino acid substitutions, additions, or deletions were not examined. Thus, the applicants have only extended an undue invitation to one practicing the invention to go out and identify suitable peptides. The disclosure does not set forth which the critical molecular determinants modulating the epitopic properties of any given peptide.

4) The art teaches that the capacity of a putative CTL epitope to bind to a class I molecule does not mean that the epitope will be immunogenic. Applicants suggestion that the testing of the various peptides encompassed by the claims was performed is inaccurate. No immunogenicity studies were performed on any peptides having any of the claimed substitutions, additions, or deletions. Moreover, the identification of a CTL response against any given peptide in the *in vitro* assay employed by applicants does not address the immunological properties of the peptide. These can only be examined by injecting the peptides into a suitable host and ascertaining if the peptides produce an HCV-specific CTL response.

emphasizes once again the importance of understanding the correlates of protective immunity before attempting to design a rational pharmaceutical or therapeutic. The art clearly demonstrates that the correlates of protective immunity against HCV infection remain to be elucidated. As previously set forth, Rehermann *et al.* (1996), observe that patients chronically infected with HCV develop HCV-specific CTL, but these CTL response are unable to clear the infection or produce any immediate salubrious effects. The authors concluded (refer to Discussion, page 1439) that "these results and the published database suggest that **the CTL response probably contributes to disease pathogenesis but is not vigorous enough to eradicate the virus during chronic HCV infection in most patients.**" Applicants' response fails to provide any evidence addressing this caveat.

9) The disclosure fails to identify the correlates of protective immunity as it pertains to HCV infection. Applicants again argue the claimed compositions need not be beneficial in all patients. Once again, this argument is misdirected and fails to address the crux of the rejection. The art clearly illustrates that the correlates of protective immunity against HCV remain to be elucidated (Koziel *et al.* ,1997; Koff, 1993; Prince, 1994). Patients, often vigorously, develop HCV-specific CTL responses, but these responses are often inadequate and incapable of clearing the virus or providing any substantial ameliorative effects. A number of factors contribute toward this inadequate immune response including the presence of HCV variants that elude immune surveillance, the presence of variant HCV CTL epitopes with altered antigen processing, transport, and presentation properties, and allelic MHC variation within any given patient population. Moreover, Koff (1993) adds that "the general failure to identify a neutralizing, protective humoral immune response in HCV infection coupled with the data described by Farci et al. represent an

awesome constellation of impediments to the development of a HCV vaccine." Applicants simply dismiss these teachings without providing any sound evidence or reasoning.

10) The disclosure fails to provide appropriate *in vitro* systems for the propagation of HCV and assays for the study of infection of cytopathic effects. Applicants fail to appreciate the significance of this statement. In order to identify putative therapeutic compounds, the skilled artisan must first have the requisite *in vitro* systems with which to propagate the infectious agent of interest and assays to determine the potential antiviral activity of any given compound. The art teaches that these systems and assays are not available to the virologist pursuing HCV antivirals (Koff, 1993 and Prince, 1994). As Koff (1993) concludes, "The list of obstacles to the development of a hepatitis C vaccine is becoming formidable. Failure to propagate HCV in tissue culture, the absence of simple in vitro assays for infection or cytopathic effects . . . are well known but not insurmountable issues." Applicants note that they can detect CTL responses in patient PBMCs to certain HCV CTL epitope-containing peptides. Applicants are reminded that none of the peptides currently being claimed were tested. Applicants are also reminded that the identification of a CTL response to any given peptide is not indicative that said peptide, when introduced into a patient, will be immunogenic and produce a CTL response of the specificity, magnitude, and duration that a positive clinical outcome can be obtained. Moreover, the in vitro assay examined fails to address the specificity, magnitude, or duration of the response. These parameters can only be assessed in carefully controlled studies. Such studies have not been performed by applicants.

4) The disclosure fails to provide adequate testing of the proposed pharmaceuticals in an art-recognized animal model. Applicants also fail to appreciate the significance of this statement. Following

the preliminary screening of putative antiviral candidates in *in vitro* assays, the skilled artisan generally employs a suitable animal model to further address concerns that are not evident or addressed by *in vitro* screening assays (i.e., pharmacological properties of the putative therapeutic). However, the art teaches that such models are not available to the skilled artisan trying to develop an anti-HCV compound (Koff, 1993). As Koff (1993) reports, "The list of obstacles to the development of a hepatitis C vaccine is becoming formidable . . . and the lack of a suitable small-animal model are well known but not insurmountable issues." Contrary to applicants' assertions, the art does not support the use of CTL vaccines. It illustrates the various pitfalls and obstacles associated with vaccine or therapeutic development in general. As noted *supra*, applicants note that they can detect CTL responses in patient PBMCs to certain HCV CTL epitope-containing peptides. Applicants are reminded that none of the peptides currently being claimed were tested. Applicants are also reminded that the identification of a CTL response to any given peptide is not indicative that said peptide, when introduced into a patient, will be immunogenic and produce a CTL response of the specificity, magnitude, and duration that a positive clinical outcome can be obtained. Moreover, the in vitro assay examined fails to address the specificity, magnitude, or duration of the response. These parameters can only be assessed in carefully controlled studies. Such studies have not been performed by applicants.

Furthermore, the declaration, and exhibits contained therein, filed 03 August, 2000, under 37 C.F.R. § 1.132 by Dr. Chisari is insufficient to overcome the rejection. The declaration states that only routine experimentation would be required to identify suitable variants. Nothing in the declaration or accompanying exhibits addresses the immunological or therapeutic properties of any given peptide. The declaration fails to provide any evidence

addressing the various concerns raised *supra*. For instance, the document fails to provide any guidance pertaining to the molecular determinants modulating protective immune responses. The document fails to provide any guidance concerning the immunological properties of the claimed peptides that has been obtained from an art-recognized animal model or suitable clinical studies. Accordingly, when all the aforementioned factors are considered *in toto*, it would clearly require undue experimentation to practice the invention as presently claimed.

Non-statutory Double Patenting

6. The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington*, 418 F.2d 528, 163 U.S.P.Q. 644 (C.C.P.A. 1969); *In re Vogel*, 422 F.2d 438, 164 U.S.P.Q. 619 (C.C.P.A. 1970); *In re Van Ornum*, 686 F.2d 937, 214 U.S.P.Q. 761 (C.C.P.A. 1982); *In re Longi*, 759 F.2d 887, 225 U.S.P.Q. 645 (Fed. Cir. 1985); and *In re Goodman*, 29 U.S.P.Q.2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. § 1.78(d). Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 C.F.R. § 3.73(b).

7. Claims 22-25, 30, 32, 36, 40, and 44-66 stand rejected under the

judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 11-33 of U.S. Patent No. 5,709,995. Applicants have indicated that a terminal disclaimer will be submitted upon the identification of allowable subject matter.

Finality of Office Action

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a). **A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.**

Correspondence

9. The Art Unit location of your application in the Patent and Trademark Office has changed. To facilitate the correlation of related papers and documents for this application, all future correspondence should be directed to **art unit 1648.**

10. Correspondence related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Official communications should be directed toward one of the following Group 1600 fax numbers: (703) 308-4242 or (703) 305-3014. Informal communications may be submitted directly to the Examiner through the following fax number: (703) 308-4426. Applicants are encouraged to notify the Examiner prior to the submission of such documents to facilitate their expeditious processing and entry.

11. Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (703) 308-2227. The examiner can normally be reached Monday through Thursday from 8:30 AM to 6:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisors, James Housel or Laurie Scheiner, can be reached at (703) 308-4027 or (703) 308-1122, respectively. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

Respectfully,

Jeffrey S. Parkin, Ph.D.
Patent Examiner
Art Unit 1648

21 March, 2001

LAURIE SCHEINER
PRIMARY EXAMINER